CANCER FACTS
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NCI Seeks Answers on Prostate Cancer: Causes, Detection, Prevention, and Treatment

The National Cancer Institute (NCI) is mobilizing resources to address important questions about the management of prostate cancer, a need that is underscored by a recent sharp rise in the reported incidence of the disease.

In 1991, the incidence of prostate cancer in U.S. men rose 25 percent above the 1990 rate, according to NCI's Surveillance, Epidemiology, and End Results (SEER) Program. The death rate from prostate cancer is also rising, though much more slowly than the incidence rate.

Prostate cancer is the most frequently diagnosed cancer (other than skin cancer) in U.S. men, accounting for 36 percent of all cancer cases. It is a distant second to lung cancer as a cause of cancer death in men. For 1995, the estimated number of new cases of prostate cancer among U.S. men is 244,000, and the estimated number of deaths from this disease is 40,000. Prostate cancer rates increase sharply with age, and more than 75 percent of cases are diagnosed in men age 65 and older. The incidence and mortality rates of prostate cancer in African American men surpass those rates in white men.

Experts believe that the increased incidence of prostate cancer is largely, if not entirely, due to increased detection and diagnosis and not to an increase in the actual number of prostate cancers. In fact, recent studies indicate that increased screening for the disease is likely a major reason for the dramatic increase in the incidence rate.

Screening methods such as serum testing for the prostate-specific antigen (PSA), digital rectal exam (DRE), and diagnostic imaging techniques, as well as increased public awareness, have led to more intensive medical surveillance of asymptomatic men. Physicians increased their use of the PSA blood test for men age 65 and older from 1,430 tests per 100,000 men in 1988 to 18,000 per 100,000 men in 1991.

Autopsy studies on men who died from causes other than prostate cancer reveal the extent of the disease in the population. These studies show that nearly one-third of men over age 50 have microscopic prostate tumors, a figure that rises with age. Approximately 16 percent of U.S. men will be diagnosed with prostate cancer during their lifetime, and 3 percent will die of this disease. Most prostate cancers never become life threatening. A majority of men who develop prostate cancer will eventually die from unrelated causes.

The possibility that many prostate tumors may remain latent for a number of years and may never cause any serious medical problems raises questions about the management of early stage prostate cancer. There is currently no way to predict accurately which early stage cancers will progress rapidly. Thus, uncertainties remain about which individuals would benefit from treatment. Moreover, available treatments are associated with varying side effects; although unlikely, death can occur, particularly among older patients.

The questions surrounding treatment of early stage prostate cancer complicate the issue of screening asymptomatic men for the disease. Given the existing level of knowledge, it is difficult to compare accurately the risks and benefits of screening. Doctors and patients need to consider the potential morbidity and mortality prevented by treatment versus the potential morbidity and mortality caused by treatment. The NCI is carrying out treatment and screening trials to address some of these questions. At this time, however, there is insufficient evidence to

establish that a decrease in mortality from prostate cancer occurs with screening by DRE, transrectal ultrasound, or serum markers including PSA. Each man should discuss the issues with his physician and, recognizing the uncertainties that may be involved, choose the best approach for himself.

Identification of methods to discriminate between aggressive and indolent (slow-growing) tumors is a very high research priority. NCI-supported scientists are searching for genetic and other biological factors that may influence the development or progression of prostate cancer. Such factors could help determine which patients are most likely to benefit from therapy and which might be better served by close medical observation. In addition, NCI is supporting research directed toward the development of new surgical, radiation, and drug therapies to improve the effectiveness and safety of prostate cancer treatment; it also supports studies of prostate cancer prevention.

The NCI spent an estimated $59 million on prostate cancer research in 1995. In addition to traditional research grants, NCI funds several Specialized Programs of Research Excellence (SPOREs) in prostate cancer. SPOREs carry out multidisciplinary research programs designed to facilitate the translation of basic research findings into clinical and public health applications, with the aim of reducing incidence and mortality and improving survival and quality of life.

Questions and Answers
Prostate Cancer: Causes, Detection, Prevention, and Treatment

1. How much has prostate cancer incidence increased?

Prostate cancer incidence (the number of new cases of prostate cancer diagnosed per year per 100,000 men) rose an average of 3.9 percent annually from 1973, the year the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program began tracking incidence, to 1991, the latest year for which rates are available. The incidence rate increased 2.2 percent per year from 1975 to 1979, and 12.1 percent per year from 1987 to 1991. The 25-percent increase from 130.6 cases per 100,000 men in 1990 to 163.0 cases per 100,000 men in 1991 is the largest recorded by SEER in a single year.

2. What are the reasons for the increase in prostate cancer incidence?

There is no evidence that changes in the distribution of risk factors are causing the increased incidence. The NCI and NCI-supported researchers are investigating known and suspected risk factors (see question 3). However, even if possible risk factors such as vasectomy are linked to prostate cancer, they are unlikely to contribute significantly to population risk to explain much of the recent large increase. Much of the increase is believed to derive from tests and procedures that purposely or incidentally detect asymptomatic cancers. A surgical procedure known as transurethral resection of the prostate (TURP), commonly used during the 1970s and 1980s to treat benign prostatic enlargement, revealed many cases of latent prostate cancer. In the 1990s, the wide availability of the PSA test, which often detects asymptomatic cancers, is likely to account for increased prostate cancer incidence.

A hospital-based survey by the American College of Surgeons reported that 68.4 percent of prostate cancer patients diagnosed in 1990 had been tested for PSA, compared with only 5.8 percent in 1984. In a recent study, NCI researchers linked SEER data with Medicare claim records from SEER's nine geographic areas to determine relationships among screening tests, TURP, and incidence rates in the general population. The researchers concluded that the increasing use of PSA screening is the most likely reason for the dramatic increase in prostate cancer incidence rates.

3. Who is at risk for prostate cancer?

Growing older is the primary risk factor for prostate cancer. The median age at diagnosis is 72 years. Racial differences are apparent: African Americans have significantly higher incidence rates than white Americans, while Asian immigrants to the United States have much lower rates.

Prostate cancer growth is stimulated by male hormones, and high hormone levels have been linked to risk for the disease in various populations. A number of genetic and

environmental risk factors have been suggested, but none has been conclusively proven, although prostate cancer tends to run in families. Fathers and brothers of patients have twice the risk of men with no affected relatives, while men with three affected relatives face an elevenfold increased risk. Researchers have found that men whose female relatives have a high incidence of breast cancer may have a higher than average risk of developing prostate cancer.

Incidence patterns in immigrant populations are observed to change over time, approaching those of the host country, which suggests environmental influences on risk, such as diet. International comparisons show generally higher rates in countries with high-fat diets, and some case-control studies also suggest a role for dietary fat, especially saturated fat found in meats and dairy products.

NCI-supported researchers recently conducted a case-control study of prostate cancer among groups in the United States and Canada who are at high risk (African Americans), moderate risk (whites), and low risk (Asian Americans) for the disease. The study assessed the contributions of diet, physical activity, and body size to the observed ethnic differences in risk. Although researchers found no consistent evidence of a relationship between prostate cancer risk and either body mass or physical activity, increased risk of prostate cancer was found to be associated with high intake of saturated fat in each of the ethnic groups studied. Other factors such as genetically determined hormone levels and diet during adolescence may account for differences in incidence among the ethnic groups studied.

Other researchers used the data collected in this study to assess whether there is a relationship between vasectomy and prostate cancer. A number of published reports have suggested that vasectomy slightly increases risk, while others have found no higher risk in men who have undergone this surgery. Data from this case-control study did not provide evidence of an association of prostate cancer risk with a history of vasectomy, age at vasectomy, or time since vasectomy. Further studies need to be done.

Other proposed risk factors for prostate cancer include a history of venereal disease, multiple sexual partners, and certain occupations, notably farming. However, evidence related to these factors is inconclusive. The NCI's Agricultural Health Study will identify and assess factors that may account for observed excesses of prostate and other cancers among farmers.

4. How much has prostate cancer mortality increased?

Relative to incidence, prostate cancer mortality (the number of deaths per year per 100,000 men) has been rising slowly—about 1 percent per year from 1973 to 1991. However, mortality has increased more rapidly in recent years: The annual rate of increase from 1987 to 1991 (2.9 percent) was more than twice the rate from 1975 to 1979 (1.2 percent). Mortality has increased most in men age 85 and older.

5. What are the reasons for the increase in prostate cancer mortality?

The reasons are unclear. Investigations are under way at NCI to determine the extent to which prostate cancer mortality trends are due to an increase in the numbers of men surviving to the oldest ages when prostate cancer is most common. (Although mortality statistics are age-adjusted to compensate for aging of the population, all men age 85 and older are grouped together.) Rapid growth in the elderly population is largely an effect of declining heart disease mortality since the late 1960s. Another possibility is that as more men are diagnosed with prostate cancer, their deaths may be attributed to the cancer even if they actually die of another cause. Finally, as-yet-unidentified factors may be contributing to a genuine increase in age-specific mortality.

6. Have prostate cancer survival rates changed?

Survival rates have improved somewhat over time. For all races combined, 5-year relative survival increased from 66.7 percent during 1974 to 1976 to 79.6 percent during 1983 to 1990. It is difficult to determine the extent to which survival increases are due to improvements in treatment. This is partly because earlier detection increases the time between diagnosis and death regardless of treatment effects—a phenomenon known as lead-time bias. In addition, more intense surveillance may be detecting tumors that would otherwise never have been diagnosed clinically.

Five-year survival rates are lower for African American men (66.4 percent during 1983 to 1990) than for white men (81.3 percent during 1983 to 1990). This difference is due in part to the fact that African American men tend to be diagnosed at later stages of the disease. But even within stages, survival rates are lower for African Americans.

7. How do prostate cancer incidence and mortality rates differ for African American men and white men?

African American men have considerably higher incidence rates (209.6 cases per 100,000 African American men in 1991) than white men (159.2 cases per 100,000 white men in 1991). African Americans may have the highest rate of prostate cancer incidence in the world. In addition, their prostate cancer mortality rate is twice as high as the rate for white Americans. In 1991, mortality rates were 24.7 cases per 100,000 white men, and 55.1 cases per 100,000 African American men. Mortality rates also are increasing much more rapidly among African American men (about 1.8 percent annually from 1973 to 1991) than among whites (about 1.0 percent annually).

8. Why are prostate cancer rates high among African American men?

The causes of higher rates of prostate cancer among African American males are largely unknown. An NCI study found that even when income and education are controlled for, African Americans have much higher rates than whites. An NCI-supported study is being conducted in three areas of the United States to investigate the reasons for African Americans' high rates of prostate cancer and other cancers. This case-control study will

examine the impact of a wide variety of potential risk factors, including dietary and other lifestyle differences, occupational exposures, and hormonal and genetic differences.

9. What is a digital rectal examination (DRE)?

In a digital rectal examination, the doctor feels the prostate through the wall of the rectum. Hard or lumpy areas may mean that cancer is present.

Some studies suggest that DRE increases the proportion of prostate cancers discovered at a localized stage. However, it has yet to be determined whether routine screening (checking for disease in men who have no symptoms) by DRE reduces prostate cancer mortality.

10. What is prostate-specific antigen (PSA)?

PSA, a protein produced by prostate cells, is frequently present at elevated levels in the blood of men who have prostate cancer. The U.S. Food and Drug Administration has approved a PSA test for monitoring prostate cancer patients after treatment and for use in conjunction with a digital rectal exam to help detect prostate cancer in men age 50 or older. However, much remains unknown about the interpretation of PSA levels, the test's ability to discriminate cancer from benign prostate conditions, and the best course of action following a finding of elevated PSA.

Because many unanswered questions surround the issue of PSA screening, the relative magnitude of its potential risks and benefits is unknown. While both PSA and transrectal ultrasound enhance detection when added to DRE screening, they are known to have relatively high false positive rates, and they may identify a greater number of medically insignificant tumors. Thus, PSA screening might lead to treatment that is not of proven benefit and that could result in morbidity (including impotence and incontinence) and mortality. It cannot be determined from earlier studies whether PSA screening will reduce prostate cancer mortality. Ongoing studies are addressing this issue.

11. What is NCI doing to evaluate prostate cancer screening?

The NCI held a workshop on prostate cancer screening June 15-16, 1993, to conduct an objective scientific review of available data, assess the current state of knowledge, and identify issues needing further research. Participants included scientists representing the entire range of clinical and basic research on prostate cancer, oncologists, urologists, and other physicians treating the disease.

The Institute is evaluating both PSA and DRE as part of the Prostate, Lung, Colorectal and Ovary (PLCO) Cancer Screening Trial, which began in 1993. The PLCO trial will screen 37,000 men ages 60 to 74, with those testing positive on either PSA or DRE receiving diagnostic followup. Cancer deaths in the screened group and an unscreened control group will be monitored to assess the impact of screening on mortality. The trial seeks to define and clarify the relationships among serum PSA levels, risk for prostate

cancer, and the actual presence and size of prostate cancer in individual men. The trial also will measure the accuracy and reliability of PSA and DRE in detecting prostate cancer in order to determine the suitability of these tests for general screening.

The Prostate Cancer Prevention Trial (see question 17) is designed to show whether finasteride (trade name Proscar®), a drug used to treat benign enlargement of the prostate, can prevent prostate cancer. The trial also is analyzing PSA levels in the trial participants. This trial will provide an opportunity to assess the accuracy of PSA and DRE in men receiving finasteride.

12. How is prostate cancer treated?

Treatment depends on the stage at which the cancer is found and on the age and health status of the patient. Surgery and radiation therapy are options for cancer that is confined to the prostate. Standard treatment involves either removal of the entire prostate gland (radical prostatectomy) or radiation therapy aimed at the pelvic area. Some patients, especially elderly men or men with unrelated severe medical problems, may choose to have no immediate treatment. There is currently no curative therapy for advanced prostate cancer; available treatments are aimed at slowing the spread of the disease and relieving symptoms. Hormone therapy is most commonly used in metastatic prostate cancer, and may include orchiectomy (surgical removal of the testicles) or drugs that reduce the effects of male hormones. Clinical trials are ongoing for patients with all stages of prostate cancer (see question 14).

13. What are the side effects of prostate cancer treatment?

Impotence is the most common long-lasting side effect of prostate cancer treatment. The introduction in the 1980s of a nerve-sparing technique for radical prostatectomy allowed preservation of sexual functioning in many patients. For many others, however, nerve sparing is not possible. Overall, radical prostatectomy cannot avoid causing impotence in 40 to 90 percent of patients, depending in part on age, extent of disease, and type of surgery. In addition, a small percentage of patients who undergo radical prostatectomy suffer total urinary incontinence as a result, and a larger percentage have intermittent dribbling caused by coughing or exertion. Radiation therapy causes impotence in about 40 to 50 percent of patients.

14. What treatments for prostate cancer is NCI testing in clinical trials?

Current clinical trials are evaluating various approaches, including the use of hormone therapy prior to either prostatectomy or radiotherapy, radiotherapy versus observation after prostatectomy, hormone therapy versus observation after radical prostatectomy, intermittent hormone therapy, and chemotherapy.

Suramin, a drug that blocks growth factors, has shown promise in initial trials against hormone-resistant prostate cancer. Because suramin has serious side effects, NCI scientists are exploring new delivery schedules aimed at decreasing toxicity, as well as

working to develop suramin analogues that may have the same therapeutic effects with lower toxicity. Lovastatin, a cholesterol-lowering drug, kills prostate cancer cells in the test tube and is now being tested in humans in an early phase trial. Other drugs in ongoing or planned clinical trials include strontium; CPT-11; topotecan; Taxol® and taxotere; didemnin B; the vitamin A derivatives (retinoids) 4-HPR and all-trans retinoic acid; and interferon, a biological agent.

Innovative delivery systems for radiation therapy are also being tested. These include radioactive implants placed inside the patient's body, as well as external beam therapy designed to decrease radiation exposure of normal tissues.

The NCI is supporting a large-scale cooperative trial with Veterans Administration medical centers to compare conventional surgery versus observation with palliative management. This PIVOT study (Prostate Cancer Intervention Versus Observation Trial) will compare mortality, morbidity, quality of life, and other outcome variables in 2,000 men with clinically localized prostate cancer. Subjects are randomized to either radical prostatectomy or expectant management, with the latter (observation) group being treated only as symptoms or cancer progression dictate. An earlier trial showed no significant difference in survival for patients assigned to surgery versus expectant management, but that study was too small to give definitive results.

15. What kinds of new prostate cancer drugs is NCI developing?

One promising drug development strategy for prostate cancer involves identifying and testing agents that interfere with growth factors and other molecules involved in cancer cells' signaling pathways. Agents under investigation include drugs that block tyrosine kinases (enzymes involved in cell signaling) or stimulate production of TGF-beta (an inhibitory growth factor). A related strategy involves inducing terminal differentiation of prostate cancer cells, the final stage of development in which mature cells cease to reproduce. Potential differentiating agents under evaluation include various retinoids and phenylacetate.

Inhibition of tumor invasion and metastasis is a potential therapeutic approach which is still in very early stages of development. The protein TIMP-2, which inhibits tumor invasion in tissue culture, is being studied as a possible treatment for bone metastasis in prostate cancer.

16. How can basic laboratory research help answer questions about the management of prostate cancer?

Although the exact genetic and biological changes leading to prostate cancer have not been defined, progress is being made in understanding some of the cellular processes involved. Advances in knowledge of the underlying biology of prostate cancer, including the roles of hormones, growth factors, oncogenes and tumor suppressor genes, and apoptosis (programmed cell death) could lead to more effective detection, treatment, and possibly prevention of the disease.

Genetic changes on chromosomes 8, 10, 16, and 17 have been associated with prostate cancer, though the genes involved have not been pinpointed. Particularly important for the management of prostate cancer would be the identification of biological and genetic factors that determine a tumor's potential to grow and cause widespread disease. Based on genetic studies of rat prostate cancer cells, NCI-supported scientists have discovered a metastasis suppressor gene. Studies are planned to analyze the functions of this gene and evaluate its potential role in determining drug responsiveness and prognosis in prostate cancer.

17. Can men do anything to help prevent prostate cancer?

Because avoidable risk factors for prostate cancer have not been identified, it is not currently possible to prescribe any primary preventive measures. However, a number of agents have entered chemoprevention trials for prostate cancer.

A large NCI-funded trial of finasteride began in 1993. This drug, which blocks the action of an enzyme involved in androgen (male hormone) metabolism, is currently used to treat benign prostate enlargement. Because androgens stimulate prostate growth, including cancer, researchers believe finasteride may prevent cancer from developing. In this study (the Prostate Cancer Prevention Trial), 18,000 men who do not have prostate cancer will be randomly assigned to receive either finasteride or placebo for 7 years, and will be followed to assess the drug's effect on the development of prostate cancer.

A phase I chemoprevention trial of the retinoid 4-HPR (4-hydroxyphenylretinamide) in men with elevated PSA levels began in 1992. Other agents that may be tested for chemoprevention include other retinoids, the cholesterol inhibitor lovastatin, selenium plus vitamin E, and aromatase inhibitors (enzymes that convert androgens to estrogens, female hormones).

18. Where can I obtain more information about prostate cancer?

The Cancer Information Service (CIS), a program of the National Cancer Institute, provides a nationwide telephone service for cancer patients and their families, the public, and health care professionals. CIS information specialists have extensive training in providing up-to-date and understandable information about cancer. They can answer questions in English and Spanish and can send free printed material. In addition, CIS offices serve specific geographic areas and have information about cancer-related services and resources in their region. The toll-free number of the CIS is 1-800-4-CANCER (1-800-422-6237).

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Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online

Internet

Use http://www.cancer.gov to reach NCI's Web site.

CancerMail Service

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service

Dial 301–402–5874 and listen to recorded instructions.

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